

Medical Staff Conference

Liver Transplantation

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *The University of California at San Francisco has had a long-standing interest in liver transplantation and has been active in research in this field. Our discussant for this conference is Dr Ira S. Goldman, who is Assistant Professor of Medicine in Gastroenterology at the University of California, San Francisco, and who performs most of his clinical duties at the San Francisco Veterans Administration Hospital. Dr Goldman's topic is the current state of liver transplantation.*

DR GOLDMAN:† It has been stated by some that the human soul resides in the liver. Whether or not that is true, it is true that the liver is an organ vital to life and, in cases of advanced liver disease, transplantation seems to offer the only hope for prolonging life. Although in the past 20 years much progress has been made, successful liver transplantation with significant prolongation of life has been difficult to achieve. Liver transplantation has only recently been put in the public spotlight, with congressional committees publicly considering funding for transplantation and television news shows devoting entire segments to the discussion of liver transplantation. I will review the current state of liver transplantation, with the hope of providing a better understanding of its background and history, indications, surgical and immunologic problems and prognosis and future prospects for those currently undergoing liver transplantation.

Two different forms of liver transplantation have been used clinically. With *orthotopic liver transplantation*, a patient's diseased liver is removed and replaced with a donor liver (homograft). In the other approach, known as *heterotopic* (or accessory) *transplantation*, a patient's liver is left in place and an extra liver is inserted at an ectopic site. Orthotopic transplantation

seems to be the more promising procedure, making up well over 90% of liver transplants thus far.¹

Welch first described the placement of heterotopic liver transplants in dogs in 1955,² and five years later orthotopic liver transplantation, also in dogs, was successfully done by Moore and colleagues.³ Since then hundreds of experimental studies in various animal species have been conducted that have contributed to our understanding of the technical problems of transplantation and the features of rejection following liver transplantation.⁴

In all species thus far studied, liver grafts are rejected less aggressively than other organs. In pigs and rats, this has been especially pronounced. In rats, the degree of rejection seems to be closely related to the similarity of the strains between donor and recipient, which suggests that immune-response genes may play an important part.^{5,6}

Furthermore, work by Zimmerman and co-workers this past year⁷ has also shown that prolonged survival of orthotopic allografts in rats is dependent on the similarity of the strains of the animals involved, indicating a range of recipient immune responsiveness to transplantation antigens. Their work further suggests that the graft itself is involved in the immunologically specific reduction of recipient alloreactivity. Both soluble major histocompatibility antigens and antigen-antibody complexes have been found in long-term surviving liver recipient rats, and it may be these complexes that possess the observed immunosuppressive properties.

The significance of this is that because the liver is rejected less aggressively than other organs, lower doses of immunosuppressive drugs are required and thus complications can be reduced considerably, especially in the pediatric age group.

Liver transplantation was first attempted in humans by Starzl at the University of Colorado in 1963. The first patient who underwent an orthotopic transplantation died, as did six others at several centers during

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

†Ira S. Goldman, MD, Assistant Professor of Medicine in Gastroenterology, University of California, San Francisco.

the next year. Consequently, clinical trials were halted for three years. In 1967 the first extended survival of a human liver recipient was achieved. The patient, an 18-month-old girl, lived for more than 13 months before dying of metastasis from hepatocellular carcinoma, the disease for which she had originally been treated.⁸

Heterotopic liver transplantation was first done clinically by Absolon and associates in 1965,⁹ but one-year survival was not achieved until 1973 by Fortner's group in New York City.¹⁰

The demonstration of its feasibility, however, did not make liver transplantation a widely used clinical procedure. Clinical trials were continued, but only on a limited basis due to the disparity between the moderate success rate and the immense requirements for personnel and financial resources. Equally prohibitive are the difficulties in defining the indications for transplantation, the lack of an artificial liver support device and the complexity and severity of surgical, immunologic and infectious problems after transplantation.

Transplant Centers

There are two major transplant centers in the world. One group is headed by Thomas E. Starzl, MD, initially working in Denver and now at the University of Pittsburgh,^{8,11} and the other, instituted in 1968 by Drs R. Y. Calne and Roger Williams, is a joint program conducted between the University Hospital at Cambridge and King's College Hospital in London.^{6,12,13}

Other centers that have reported six or more cases include those headed by Pichlmayr in Hanover, West Germany, with 68 cases¹⁴; Krom in Groningen, Holland, with 18 cases¹⁵; Houssin in Paris; Wolff in East Germany and Hong in the Republic of China. In the United States, clinical transplant programs are also active at the University of Minnesota and the University of Tennessee.⁸

Indications and Contraindications

In theory, any patient dying of liver disease might benefit from a liver graft, but in practice some general criteria, such as the factor of age, have emerged. Whereas Starzl's group considers children as well as adults under 50 years of age as potential candidates,^{8,11} Calne and Williams have avoided pediatric transplants because of a shortage of pediatric liver donors and the side effects of long-term steroid use in this population, and they recommend assessing biologic rather than chronologic age in their adult patients.^{6,12}

Older patients are not considered good risks, as they frequently cannot withstand the side effects of the intensive immunosuppression. The prospects for treating children with a variety of liver disease have improved, however, since the risks of long-term, high-dose steroid therapy have been reduced with newer immunosuppressive agents, such as cyclosporine.

The major contraindications to transplantation include portal vein thrombosis, metastatic carcinoma, major systemic infection and systemic arterial hypo-

TABLE 1.—*Indications for Orthotopic Liver Transplantation in 103 Adult Patients**

	Percent Patients
Cirrhosis	47
Primary biliary cirrhosis (N=13)	
Cryptogenic (N=11)	
Chronic active hepatitis (N=9)	
Sclerosing cholangitis (N=4)	
Alcoholic (N=4)	
Secondary biliary cirrhosis (N=3)	
Other (N=4)	
Primary hepatoma	34
Cholangiolar carcinoma	7
Hepatic metastasis	5
Budd-Chiari syndrome	5
Extrahepatic biliary atresia	2

*Cambridge/King's College Hospital Series, from Williams et al.¹³

tension. Relative contraindications include alcoholism, as alcoholic patients tend to be unreliable; extensive prior abdominal operations because of adhesions; acute fulminant liver failure because the prognosis is so difficult to assess and the operative risks too high, and liver disease not severe enough to warrant transplantation.⁸ Hepatitis B surface antigen positivity in a recipient is not a contraindication to transplantation¹⁶; however, chronic hepatitis B infection has recurred even with the use of hyperimmune globulin at the time of transplantation.

Adults

In adults, most liver grafts have been done in patients who have nonmalignant, nonalcoholic cirrhosis. The most common indications among adult patients with cirrhosis in Calne's series are primary biliary cirrhosis, cryptogenic cirrhosis and chronic active hepatitis (Table 1).¹³ The other major category is primary malignancy of the liver. Although the incidence of tumor recurrence is almost 60%, results have been especially favorable in the fibrolamellar form of hepatoma, which seems to be late in spreading.^{8,16-18} Patients who have cholangiocarcinoma that is confined solely to the liver may also be considered for transplantation. The indications for carrying out liver transplantation in adults in Starzl's series are very similar to those of Calne and Williams.

Children

In children, liver transplantation has been done most commonly for biliary atresia, chronic active hepatitis and hepatic-based inborn metabolic diseases (Table 2).¹⁹ What is particularly intriguing about the hepatic-based metabolic diseases is that cures have been effected with transplantation. Success has been achieved with several such metabolic diseases as α_1 -antitrypsin deficiency, hereditary tyrosinemia, sea-blue histiocyte syndrome and Wilson's disease.

In Starzl's series,²⁰ all four patients with α_1 -antitrypsin deficiency assumed the normal donor phenotype or

their serum α_1 -antitrypsin returned to normal levels after transplantation. One patient with glycogen storage disease had normal carbohydrate metabolism postoperatively. Normalization of serum tyrosine and urinary metabolites occurred in a patient who had hereditary tyrosinemia, and patients with sea-blue histiocyte syndrome and Wilson's disease each had reduction of neurologic deficits.

Timing of Transplantation

Because of the risks involved in transplantation, the timing of the operation requires careful thought. A patient's disability from liver disease should be great enough and the prognosis so limited that, in comparison, the risks of transplantation become acceptable. On the other hand, by the time a patient shows signs of advanced liver failure, the chances of surviving a surgical transplant procedure may be greatly reduced.¹⁶ Still, more than 50% of those accepted for liver grafting die before a donor liver becomes available.⁶

Much of the difficulty in determining when to transplant would be reduced if accurate tests of hepatic

reserve or those of true liver *function*, analogous to the creatinine clearance for assessing renal function, were available. There is, however, no equivalent simple way to measure hepatic function or reserve. Similarly, there is no artificial hepatic support device analogous to the kidney dialysis machine; if such a device existed, we would have the luxury of attempting liver transplantation under much more controlled conditions.

Preoperative evaluation requires an in-hospital investigation. In the case of cirrhosis, it is essential to determine that the portal vein is patent by using mesenteric angiography or splenoportography; thrombosis of the portal vein is a contraindication to transplantation. In cases of malignancy, the diagnosis of primary malignancy of the liver must be confirmed histologically, and involvement of both lobes confirmed; otherwise, partial hepatic resection would be the procedure of choice. Chest and bone radiographs, radionuclide bone scans, lymphangiography and computed tomography have been recommended as part of the work-up to exclude extrahepatic metastasis.¹⁶

Of about 500 orthotopic liver transplants that have been done worldwide to date, more than 400 have been done by Starzl's and Calne's groups. As can be seen from Starzl's recent experience of the past year or two (Figure 1), the number of transplantations being carried out is increasing rapidly.⁸

The urgent need of most patients receiving a liver transplant and the time constraints of liver preservation have precluded systematic attempts at tissue typing.⁸ With the random donor-recipient pairing thus far used, good matches at the human leukocyte antigen (HLA)-A, B and DR loci have not been obtained. Hepatic transplantation has been done without adverse effect in the presence of recipient antidonor antibodies, which cause hyperacute rejection in renal homografts.²¹ ABO blood group transfusion principles are generally accepted practice. Starzl has reported a few cases of transplantation across ABO blood groups,⁸ though this is rarely necessary.

Donor Operation

Procuring a sufficient number of donor livers has been one of the most significant problems for the groups attempting transplantation, in common with those attempting renal transplantation.²² Although the kidneys are not compromised by liver removal, there has been some reluctance on the part of those transplanting or procuring kidneys to have the liver removed from the same donor.²³ The removal of the donor liver is an operation that itself takes two to three hours.

Since the acceptance of brain death criteria, well-preserved organs can be obtained that are relatively free from the damages of ischemia. Starzl preserves livers by rapidly perfusing them with a cold electrolyte (Collins') solution and has stored them up to 12 hours.⁸ Calne's group uses a plasma protein solution and has stored donor livers for up to ten hours.⁶

Because bile is such an irritating substance, espec-

TABLE 2.—Indications for Transplantation in 112 Pediatric Patients (≤ 18 yrs)*

	Percent Patients
Biliary atresia	55
Inborn metabolic errors	19
Chronic aggressive hepatitis	13
Neonatal hepatitis	3
Secondary biliary cirrhosis	3
Hepatoma	3
Congenital hepatic fibrosis	1
Others	3

*From Malatack et al.¹⁹

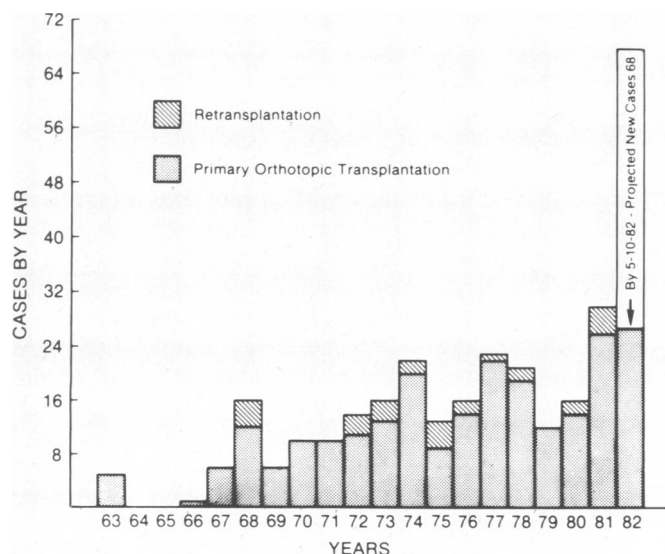


Figure 1.—Yearly number of liver transplantations at the University of Colorado (1963 to 1980) and the University of Pittsburgh (1981 to 1982). (Reproduced from Starzl et al⁸ with permission of the authors and publisher.)

ally to ischemic tissue, bile is removed from the large bile ducts and gallbladder by irrigation with cold plasma to prevent sloughing of biliary mucosa from bile left in the biliary tract.

Recipient Operation

The recipient operation is technically the most difficult, and is also the most dangerous hurdle a patient has to overcome.⁸ The diseased liver is removed following cross-clamping and dividing the hepatic artery, portal vein and inferior vena cava above and below the liver. The more recent use of venous bypass from femoral to upper extremity or jugular vein, and an intervening oxygenator, has minimized problems related to hemodynamic instability during cross-clamping of the major vessels.

Size matching of the donor liver to the recipient is important to prevent mechanical respiratory compromise and to permit closure of the abdomen. Vascular reanastomosis is accomplished first, followed by reconstruction of the biliary tree. The spleen was removed in most of the patients transplanted before 1979, in

part to achieve better immunosuppression, but mainly to relieve hypersplenism and leukopenia that prevented the use of azathioprine or cyclophosphamide. With the advent of cyclosporine, formerly called cyclosporin A, splenectomy has been mostly discontinued.

Biliary tract reconstruction was considered the most difficult part of liver grafting and accounted for most fatal complications in early trials.¹ The incidence of bile fistula and biliary obstruction leading to sepsis has been reduced with modern techniques. Starzl considers duct-to-duct anastomosis with a T-tube stent, as illustrated in Figure 2-A, to be the procedure of choice. When this is not feasible, such as in cases of biliary atresia wherein the recipient residual bile duct is short, the duct is anastomosed to a Roux limb of jejunum, as shown in Figure 2-B.⁸

Since 1976 Calne has used a technique in which the homograft common duct and gallbladder are anastomosed into a common channel or conduit, and then connected either to the recipient common duct or a Roux limb of jejunum.²⁴

Perioperative Complications

Operative complications accounted for the poor survival rates in early trials, some of which are listed in Table 3.¹⁶ Hemorrhage could be massive, and patients often received as many as 50 units of blood during a single transplant procedure. Hypotension and the need for venous bypass after clamping the major vessels have been mentioned. Life-threatening hyperkalemia occurred intraoperatively due to massive efflux of potassium into the systemic circulation because of ischemia of either the recipient or the donor liver. Vascular anastomoses frequently clotted; air embolism with severe neurologic sequelae from air left in the donor liver, and donor-recipient size mismatch were but a few of the early problems.

Postoperative complications can be broken down into an early and a late phase as shown in Table 3.¹⁶ Some of these have already been alluded to. Sepsis and opportunistic infection were major causes of death in half of Starzl's first 93 patients. At autopsy, almost 20% had evidence of systemic fungal infection.²⁵

Gastrointestinal hemorrhage occurred in 23% of Starzl's first 150 patients, with a mortality of 85%.²⁶ Peptic ulcer disease was the most frequent cause. Intestinal perforation from biliary anastomoses now occurs less frequently, and respiratory insufficiency from an oversized homograft has been mentioned.

All of the above perioperative complications are potentially reversible except for ischemic injury of the homograft or early loss of its blood supply. In such cases, retransplantation is the only hope.

Late complications include rejection (both acute and chronic), biliary obstruction, sepsis, tumor recurrence and recurrent hepatitis.

Immunosuppression

Initially, immunosuppression in liver transplant recipients was accomplished using the same regimen as

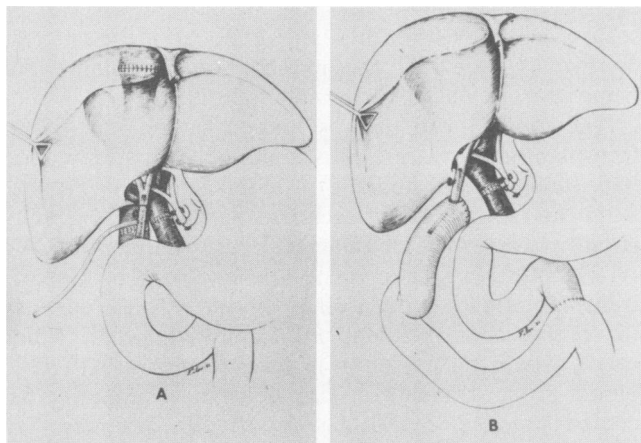


Figure 2.—Completed orthotopic liver transplantation. (A) Biliary tract reconstruction with choledochocholedochostomy. (B) Biliary reconstruction with choledochojejunostomy, using a Roux limb. (Reproduced from Starzl et al,⁸ with permission of the authors and publisher.)

TABLE 3.—Operative and Postoperative Complications*

Operative	
Hemorrhage	Vascular anastomosis
Hypotension	Air embolism
Hyperkalemia	Donor-recipient size mismatch
Postoperative	
Early	Late
Biliary obstruction plus fistula	Rejection (acute and chronic)
Sepsis and opportunistic infection	Biliary obstruction
Gastrointestinal hemorrhage	Sepsis and opportunistic infection
Intestinal perforation	Tumor recurrence
Respiratory insufficiency	Recurrent hepatitis
Irreversible ischemia	

*From Grendell.¹⁶

TABLE 4.—*Clinical Immunosuppressive Drug Regimens**

	Year of Study
Azathioprine and steroids	1963
Thoracic duct drainage as adjunct	1963
Antilymphocyte globulin as adjunct	1966
Cyclophosphamide substitute for azathioprine	1970
Cyclosporine (cyclosporin A) alone	1978
Cyclosporine and steroids	1980

*From Starzl et al.⁸

for kidney transplants. "Double-drug" therapy with azathioprine and prednisone was the first successful immunosuppressive regimen used. Between 1963 and 1980, several alternative programs were introduced (Table 4), all of which were essentially modifications of the original azathioprine-prednisone regimen.⁸ Thoracic duct drainage, antilymphocyte globulin and substitution of azathioprine with cyclophosphamide were all tried. Although rejection had generally been fairly well controlled with these regimens, the immunosuppressive therapy frequently led to septic complications. New and more promising hope for reducing the risks of immunosuppression came with the discovery of cyclosporine.

Cyclosporine is an extract from the fungi *Cylindrocarpum lucidum* and *Trichoderma polysporum*. It was first used clinically by Calne and White,²⁷ who quickly discovered its adverse side effects, namely those of nephrotoxic and hepatotoxic reactions. Both of these appear to be dose-related and reversible.²⁸ Hepatotoxic response, which occurs in about 20% of cases, is rarely serious enough, however, to necessitate discontinuation of the drug.²⁹

Cyclosporine acts by depressing both humoral and cellular immunity, with a preferential and quick reversible action against T lymphocytes. These effects are not accompanied by the bone marrow depression that so frequently limits the doses of azathioprine and cyclophosphamide.

Calne and Williams usually wait until renal and hepatic function have stabilized before starting a regimen of cyclosporine, which permits a reduction in steroid dose to as low as one fifth of the prior dose used. Starzl, on the other hand, starts giving his patients cyclosporine on the day before the operation, along with large but rapidly tapered doses of prednisone. Doses are individualized so as to control rejection but minimize side effects.⁸

Rejection

Rejection of homografts still occurs, despite the use of any of the immunosuppressive regimens. This is particularly important because histologically recognizable rejection occurs in up to 50% of cases. There are no reliable liver function tests for expeditiously diagnosing functional failure of a homograft nor is there an artificial support device or readily available second organ (as with the kidney) to rely on when a homograft fails.

The clinical signs and symptoms of rejection are nonspecific and include fever, vague upper abdominal pain and loss of appetite. Ascites and hepatomegaly are often found on physical examination. Laboratory findings are equally nonspecific and include elevations in the serum bilirubin, alkaline phosphatase and aminotransferase values and prothrombin time. Radionuclides, such as those used in liver scanning, are poorly concentrated.⁸

Because all of these findings are so nonspecific, differential diagnosis from biliary obstruction, viral hepatitis or recurrence of an underlying disease (such as primary biliary cirrhosis) is at times difficult. The distinction is clearly important, however, as rejection requires *increased* immunosuppression, whereas biliary obstruction or viral hepatitis could have disastrous results unless immunosuppression is *decreased* and appropriate interventions made. Radiographic visualization of the biliary tree to rule out obstruction is mandatory before increasing immunosuppression. Similarly percutaneous needle biopsy of the liver has been invaluable in distinguishing rejection from other diseases.¹⁶

Characteristic findings of liver transplant rejection include infiltration of portal triads by mononuclear cells, mild centrilobular necrosis with bile stasis and destruction of small bile ducts in a pattern suggestive of primary biliary cirrhosis. As rejection progresses, further hepatocyte loss, fibrosis and arterial intimal thickening occur, all of which become characteristic of chronic rejection. Fennell and colleagues³⁰ have recently described the histologic similarity of nonsuppurative destructive cholangitis seen in chronic rejection of human liver allografts, primary biliary cirrhosis and chronic graft versus host disease. Earlier reported recurrence of primary biliary cirrhosis after transplantation³¹ may have been the nonsuppurative destructive cholangitis associated with chronic rejection.

Survival Rates

Starzl attributes the recent pronounced improvement in his results to the use of cyclosporine and divides his results into the precyclosporine and postcyclosporine eras. The 170 operations done between 1963 and 1979 were reported by Starzl as three separate series. All patients were treated with azathioprine and steroids, or a variety of other adjuvant treatments as outlined earlier. Of these 170 patients, the one-year survival averaged 33%, and of these one-year survivors, 41% died in the next year and 59% lived for between 2.5 and 13 years; 20 patients have survived for more than five years.⁸

Half of these same 170 patients were younger than 18 years and, for unexplained reasons, this group had a 10% survival advantage when conventional immunosuppressants were used. Since the introduction of cyclosporine, however, survival rates of the two groups have been comparable.

Since the introduction of cyclosporine in 1980, almost 100 patients have received liver transplants, 67

of which are well documented (see Figure 3, top line). The middle line represents the 170 patients in the three series before the introduction of cyclosporine; the bottom line shows the survival of patients in Calne and Williams's series.

In the cyclosporine series, most of the deaths occurred in the perioperative phase. The actuarial survival of cyclosporine-treated patients has *doubled* the observed survival in the pre-cyclosporine era, with a current one-year survival rate of about 70%.⁸

Retransplantation

What is done if a transplant fails? With the lack of an artificial hepatic support device, *retransplantation* is the only alternative. In all, 27 patients since 1968 have been regrafted. Two patients have received three orthotopic liver grafts. Unfortunately, only 6 of these 27 patients have had significant prolongation of life with retransplantation.⁸

In Calne and Williams's series,¹² 127 livers had been transplanted as of the end of 1982, with an experience

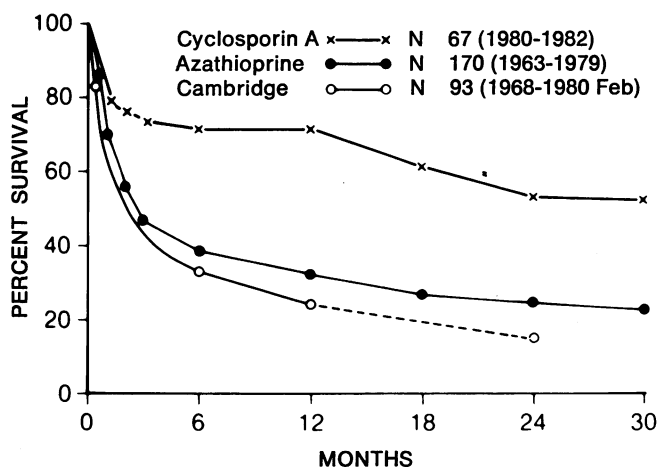


Figure 3.—The actuarial survival of patients treated with cyclosporin A (cyclosporine) and low-dose steroids compared with the actual one-year survival obtained with conventional immunosuppression (azathioprine) by Starzl and by Calne. (Reproduced from Starzl et al,⁸ with permission of the authors and publisher.)

roughly parallel to that of Starzl. In all, 16 patients are living after more than a year and four patients longer than five years. Their longest survivor is alive seven years after transplantation.

In Pichlmayr's series¹⁴ in Hanover, 68 orthotopic transplantations have been done in 65 patients, most within the past three years. Their transplantation data were divided into two categories (Table 5): those patients undergoing liver transplantation for tumor and those for cirrhosis. Of 20 patients in whom extrahepatic tumor was detected at the time of operation, only one survived for more than six months. In the other 17 patients without metastasis, four have survived more than one year. In the group with cirrhosis, those in whom transplantation was done under emergency conditions did not do as well as those who underwent more elective operations. Survival in the group with liver tumors confined to the liver was similar to that in the cirrhotic group in fair condition. An interesting observation from this group is that the patients who had cirrhosis seemed to undergo more severe rejection than those who had tumor.

In Krom's series in Holland,¹⁵ 18 liver allografts were done between 1979 and the middle of 1982. In all, 13 patients are alive, of whom 4 survived for more than a year and 3 for more than two years. These results were achieved with conventional immunosuppression without the use of cyclosporine. This group is the only one, however, that has used selective *bowel decontamination*, consisting of administering broad-spectrum antibiotics as well as polymyxin B sulfate and amphotericin B before the surgical procedure. Krom attributes the reduced incidence of Gram-negative sepsis and systemic fungal infection and their improved survival rates to this decontamination regimen.

The collective experience in liver transplantation at all centers has shown a trend toward improved survival rates, as is now evident in the fact that for patients who survive the complications of the operative and perioperative periods, the one-year survival is about 70%. Furthermore, survival rates with those undergoing transplantation for primary hepatic malignancy (without metastasis) is similar to that found in patients who have cirrhosis, and survival rates have become com-

TABLE 5.—Liver Transplantation Results in Patients With Tumor and Those With Cirrhosis*

	No. of Patients	Survival Time (months)				Alive	Longest Survivor
		1	1-6	6-12	>12		
<i>Tumor</i>							
Extrahepatic growth	20	8	7 (4)	4 (—)	1 (—)	(4)	2 yr
No extrahepatic growth	17	5	2 (1)	6 (2)	4 (4)	(7)	6.75 yr
<i>Cirrhosis</i>							
Emergency operation	19	15	2 (2)	1 (1)	1 (1)	(4)	3.25 yr
Fair condition	9	1	1 (1)	2 (1)	5 (5)	(7)	19 mos

*From Pichlmayr et al.¹⁴ Numbers in parentheses represent patients alive at time of publication of Pichlmayr's paper.

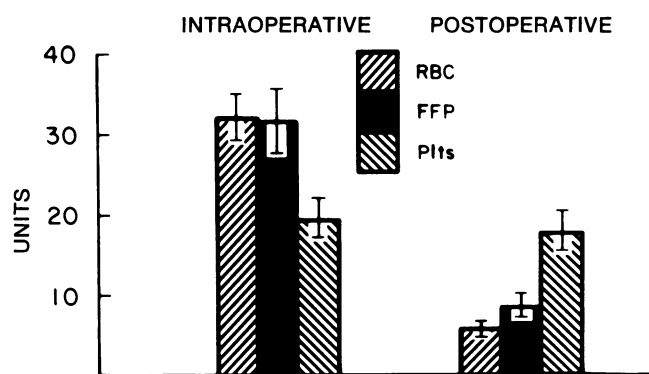


Figure 4.—Blood products used during and following liver transplantation. Bars represent means; brackets represent standard error. RBC=erythrocytes, FFP=fresh frozen plasma, Plts=platelets. (Reproduced from Van Thiel et al,¹¹ with permission of the authors and publisher.)

parable in adults and children since the introduction of cyclosporine.

Heterotopic Transplantation

Heterotopic grafting, an alternative to orthotopic transplantation, involves attaching an extra liver and leaving the patient's diseased liver in place. This all seems logical enough, but of nearly 50 well-documented heterotopic transplants, only two have had long-term success.¹⁰ Theoretically, in such cases the extra liver could be construed as a temporary support organ, which can be removed later. Unfortunately, what happens clinically is that most of these accessory livers atrophy.³²

The two primary indications for heterotopic liver transplantation are (1) small or shrunken livers, such as are seen in nonmalignant cirrhosis or biliary atresia, and (2) fulminant, self-limited disease, such as in patients with severe viral or chemical hepatitis.

One of the major by-products of research on heterotopic transplantation has been new insight into the effects of portal blood and its so-called *hepatotrophic substances* on the liver's structure, function and its ability to regenerate. These factors, which include insulin, glucagon and epidermal growth factor³³ among others, profoundly influence liver growth and regeneration.

Conclusion

Liver transplantation, especially since the introduction of cyclosporine, has become a potentially viable form of therapy. Whether the long-term results with cyclosporine continue to be as good as the initial ones remains to be seen. There are, however, some important unanswered questions: Which patient should undergo liver transplantation and when? Why are livers rejected less aggressively than other organs, and why is it that, in some species, the liver seems to be immunologically privileged? What kinds of liver function tests must be developed so that hepatic function of the recipient and donor livers can best be quantitated?

And, can a temporary artificial hepatic-support device be developed?

Funding of liver transplantation is a major question. As in the past, funding is still piecemeal at best. Much of the original work was done under grants from the National Institutes of Health (NIH). Third-party payers have been inconsistent in deciding whether liver transplantation represents accepted therapy or an experimental approach. More recently, families have had to turn to individual fund-raising appeals to fund transplants for one of their members.

What is unquestionable is that hepatic transplantation should not be undertaken without full institutional commitment. The requirements for a liver transplantation program are broad: intensive-care unit beds, operating room facilities and personnel must be available at short notice; in-hospital beds and outpatient follow-up facilities must be available; medical and nursing staff must be committed to the program, and social and psychiatric support services are very much needed.¹¹ The drain on an institution's blood bank for a single transplant patient alone can be staggering. Figure 4 shows the *average* blood product use in transplantation.¹¹ One can well imagine the quantity of blood products used when one contemplates attempting even three or four transplantations a month, as Starzl's group hopes to achieve.

While the approximate cost of a liver transplantation in Pittsburgh has averaged \$55,000 with a range between \$23,000 and \$150,000,⁸ Starzl states that dying of end-stage liver disease without the hope of recovery may be even more expensive. O'Donnell and associates³⁴ in 1980 reported that in Boston the average cost of treating a patient with variceal hemorrhage was \$35,000, and the use of any operative procedure increased the total to \$53,000. At the University of Pittsburgh, the costs incurred during repeated hospital admissions of these patients, before transplantation, exceeded those incurred by transplantation itself. What is currently unknown is what the yearly follow-up costs in caring for transplant patients will be, and what economic impact this technology will have on our health care system.

There will be increasing public pressure to do liver transplantation. It is estimated by Starzl that within five to ten years, every major center for the study of liver disease will have either liver transplantation capabilities or direct access to this kind of service, and that at least 20 centers will be needed in the United States alone.⁸ However, whether this can or should be achieved needs to be examined. These issues were explored at a recent NIH Consensus Conference on Liver Transplantation.³⁵ Useful data comparing the effectiveness of transplantation with standard medical therapy are needed. It is hoped that the NIH consensus conference and prospective clinical trials will provide some of these answers.

REFERENCES

1. Starzl TE, Koep LJ, Halgrimson CG, et al: Fifteen years of clinical liver transplantation. *Gastroenterology* 1979 Aug; 77:375-388

LIVER TRANSPLANTATION

2. Welch CS: A note on transplantation of the whole liver in dogs. *Transplant Bull* 1955; 2:54-55
3. Moore RD, Smith LL, Burnap TK, et al: One-stage homotransplantation of the liver following total hepatectomy in dogs. *Transplant Bull* 1959; 6:103-107
4. Kamada N, Calne RY: A surgical experience with five hundred thirty liver transplants in the rat. *Surgery* 1983 Mar; 93:64-69
5. Kamada N, Davies HFS, Roser B: Reversal of transplantation immunity by liver grafting. *Nature* 1981; 292:840-842
6. Calne RY: Liver grafting. *Transplantation* 1983 Feb; 35:109-111
7. Zimmerman FA, Knoll PP, Davies HFS, et al: The fate of orthotopic liver allografts in different rat strain combinations. *Transplant Proc* 1983 Mar; 15:1272-1275
8. Starzl TE, Iwatsuki S, Van Thiel DH, et al: Evolution of liver transplantation. *Hepatology* 1982 Sep; 2:614-636
9. Absolon KB, Hagihara PF, Griffen WO Jr, et al: Experimental and clinical heterotopic liver homotransplantation. *Rev Int Hepat* 1965; 15:1481-1490
10. Fortner JG, Yeh SDJ, Kim DK, et al: The case for and technique of heterotopic liver grafting. *Transplant Proc* 1979 Mar; 11:269-275
11. Van Thiel DH, Schade RR, Starzl TE, et al: Liver transplantation in adults. *Hepatology* 1982 Sep; 2:637-640
12. Calne RY: Recent advances in clinical transplantation of the liver and pancreas. *Transplant Proc* 1983 Mar; 15:1263-1268
13. Williams R, MacDougall BRD, Calne RY: Liver transplantation: Current status. *Compr Ther* 1982 May; 8:24-27
14. Pichlmayr R, Brolsch CH, Neuhaus P, et al: Report on 68 human orthotopic liver transplantations with special reference to rejection phenomenon. *Transplant Proc* 1983 Mar; 15:1279-1283
15. Krom RAF, Gips CH, Newton D, et al: A successful start of a liver transplantation program. *Transplant Proc* 1983 Mar; 15:1276-1278
16. Grendell JH: Hepatic transplantation and resection, chap 51, *In* Zakim D, Boyer TE (Eds): *Hepatology: A Textbook of Liver Disease*. Philadelphia, WB Saunders, 1982, pp 1274-1283
17. Iwatsuki S, Klintmalm GBG, Starzl TE: Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. *World J Surg* 1982 Jan; 6:81-85
18. Calne RY: Liver transplantation for liver cancer. *World J Surg* 1982 Jan; 6:76-80
19. Malatack JJ, Zitelli BJ, Gartner JC, et al: Pediatric liver transplantation under therapy with cyclosporin A and steroids. *Transplant Proc* 1983 Mar; 15:1292-1296
20. Zitelli BJ, Malatack JJ, Gartner JC, et al: Orthotopic liver transplantation in children with hepatic-based metabolic disease. *Transplant Proc* 1983 Mar; 15:1284-1287
21. Iwatsuki S, Iwaki Y, Kano T, et al: Successful liver transplantation from crossmatch-positive donors. *Transplant Proc* 1981 Mar 13(1 pt 1):286-288
22. Waltzer WC: Procurement of cadaveric kidneys for transplantation. *Ann Intern Med* 1983 Apr; 98:536-539
23. Shaw BW, Halcala T, Rosenthal JT, et al: Combination donor hepatectomy and nephrectomy and early functional results of allografts. *Surg Gynecol Obstet* 1982 Sep; 155:321-325
24. Calne RY, Williams R, Lindop M, et al: Improved survival after orthotopic liver grafting. *Br Med J* 1981 Jul; 283:115-118
25. Fennell RH, Roddy HJ: Liver transplantation: The pathologist's perspective. *Pathol Ann* 1979; 2:155-182
26. Koep LJ, Starzl TE, Weil R: Gastrointestinal complications of hepatic transplantation. *Transplant Proc* 1979 Mar; 11:257-261
27. Calne RY, White DJG: The use of cyclosporin A in clinical organ grafting. *Ann Surg* 1982 Sep; 196:330-337
28. Klintmalm GBG, Iwatsuki S, Starzl TE: Nephrotoxicity of cyclosporin A in liver and kidney transplant patients. *Lancet* 1981 Feb; 1:470-471
29. Klintmalm GBG, Iwatsuki S, Starzl TE: Cyclosporin A hepatotoxicity in 66 renal allograft recipients. *Transplantation* 1981 Dec; 32:488-489
30. Fennell RH, Shikes RH, Vierling JM: Relationship of pretransplant hepatobiliary disease to bile duct damage occurring in the liver allograft. *Hepatology* 1983 Jan; 3:84-89
31. Neuberger J, Portmann B, MacDougall BRD: Recurrence of primary biliary cirrhosis after liver transplantation. *N Engl J Med* 1982 Jan; 306:1-4
32. Starzl TE, Terblanche J: Hepatotrophic substances, chap 7, *In* Popper H, Schaffner F (Eds): *Progress in Liver Disease*, Vol 6. New York, Grune & Stratton, 1979, pp 135-152
33. Leffert HL, Koch KS, Lad PJ, et al: Hepatocyte growth factors, chap 3, *In* Zakim D, Boyer TE (Eds): *Hepatology: A Textbook of Liver Disease*. Philadelphia, WB Saunders, 1982, pp 64-75
34. O'Donnell TF, Gembarowicz RM, Callow AD, et al: The economic impact of acute variceal bleeding: Cost-effectiveness implications for medical and surgical therapy. *Surgery* 1980 Nov; 88:693-701
35. Research News: Liver transplants endorsed, reviewed by G. Kolata. *Science* 1983 Jul 8; 221:139